REMARKS/ARGUMENTS

Claims 34 – 36 and 38 – 50 are pending in the application. Claims 46 – 50 are withdrawn as drawn to a non-elected invention, pursuant to a restriction requirement.

A Request for Continued Examination (RCE) is filed concurrently with this Response.

Claims 34 – 36, 38 – 42 and 44 stand rejected under 35 U.S.C. §103(a) as unpatentable over **Kanios** (U.S. 2002/0004065).

In response to our arguments previously provided, the Examiner asserts:

> "Applicants never indicate what the field of endeavor for either the instant claims or Kanios is."

The Applicants traverse said Examiner's deduction since actually this has been discussed at pages 5 – 7 of Applicants' previous response, where the field of endeavor of the present invention was clearly identified by indicating that the claimed **devices are designed to make possible the use of rifaximin** "outside the intestine (e.g., in the oral and pharyngeal or nasal cavity, in the rectum and vagina). In particular, they allow high-level, constant in time, of concentration of rifaximin in aqueous body fluids **avoiding the intense red color** that it produces in the neighboring of the place of [administration]." (par. [0007]) [emphasis added]

Indeed, the field of endeavor was already well reported at par. 0003 – 0004 of the current

application, where it is stated that:

> "[0003] Moreover chronic infections in the oral cavity are absolute insensitive to systemic treatment by means of antibiotic. One of the scopes of present the invention is to supply adequate means for the protection of the masticator apparatus and drug delivery in the oral cavity, using material adapted for this purpose."
>
> "[0004] [R]ifaximin is known like a powerful and effective antibiotic to wide number of pathogenic agents. Its use is currently relegated to the treatment of the diarrheas and internal infections. One characteristic that renders precious such an antibiotic is that it does not permeate through the mucosae. This fact allows a local use of such an antibiotic at high concentrations, with a great efficacy, a null systemic concentration and therefore collateral effects. On the other hand, the rifaximin possesses a very low solubility in the physiological liquids. For this reasons it remains in form of small crystal, of intense red color, dispersed in the place of somministration [administration]. For aesthetic reasons, this fact prevents its use in all those places, like the mouth, where the patient wishes to maintain a socially acceptable aspect. Moreover, the drug in the form of small crystals, generates a peaky of concentration, at the moment of the application but then it disperses itself quickly far away where it is placed losing its effectiveness. In truth, a continuous and calibrated delivery along the time of rifaximin would be a very good tool for the treatment of a wide ensemble of gram-positive and gram-negative bacteria and it renders possible its use outside of the intestine." [emphasis added]

Thus, the current invention relates to a device for controlled local delivery of rifaximin, where "local delivery" means "topical delivery." As a matter of fact, as above reminded, Rifaximin allows a local use of such an antibiotic at high concentrations, with a great efficacy, a null systemic concentration and therefore collateral effects. This means that **no** transdermal delivery takes place, as further discussed herein below.

Conversely, the device for transdermal delivery of Kanios has been designed to achieve substantially zero order of the drug release profile, **independently of the type of drug in use**, even if indeed only hormones have been tested.

Therefore, the Applicants maintain the opinion that the fields of endeavor are unavoidably and unambiguously different.

Furthermore, as already pointed out in our previous response as well as already acknowledged by the Examiner, "Kanios does not explicitly prepare a composition with rifaximin and PVA." This means that **Kanios pertains to a different field of endeavor AND fails to disclose both the most relevant technical features of the currently claimed device.**

In this regard, the Examiner affirms that:

> "Merely because a reference does not explicitly teach the claimed combination of polyvinyl alcohol and rifaximin, the reference taken as a while renders obvious the claimed combination. The teachings of a reference are not limited to the examples but are prior art for all that they disclose." (page 4, last paragraph).

The Applicants indeed provided in our previous response a wide explanation of the teaching of Kanios as a whole, considering in detail each relevant aspect. As a matter of fact, it has been clearly highlighted that Kanios gives an **expressly and purposely unlimited list of possible active agents** to be delivered; i.e., par. [0056] to par. [0349], confirming that **the device concerned is absolutely independent of the drug**. This is actually declared and corroborated by Kanios himself at the following paragraphs:

> "[0056] The term "active agent" (and its equivalents "agent," "drug," "medicament" and "pharmaceutical") is intended to have the broadest meaning and includes at least one of any therapeutic, prophylactic, pharmacological or physiological active substance, cosmetic and personal care preparations, and mixtures thereof, which is delivered to a mammal to produce a desired, usually beneficial, effect. More specifically, any active agent that is capable of

producing a pharmacological response, localized or systemic, irrespective of whether therapeutic, diagnostic, cosmetic or prophylactic in nature, is within the contemplation of the invention. It should be noted that the active agents can be used singularly or in combinations and mixtures.

"[0057] There is no limitation on the type of active agent that can be used in this invention. However, active agents that are solid or crystalline at room temperature are preferred over liquid drugs, especially nicotine. Moreover, drug forms other than the free base form are also preferred." [emphasis added]

This is even more clear when considering that in all said par. [0056] to par. [0349], each drug class listed therein is followed by the term "such as" (e.g. par. [0075] "11. Anesthetics such as..."), thus only presenting drugs by way of example.

Therefore, the fact that at column 7, **Rifaximin is randomly listed among dozens of antibacterial drugs, is not more than an accidental case.**

The same applies to PVA, which is just cited at par. [0046] giving as crystallization inhibitor, a further **unlimited list** of possible substances, while being expressly stated that any absorptive agent capable of absorbing and holding water or moisture can be used. However, in the subsequent paragraphs [0047] to [0053], as well as in all the reported Examples 1 – 9, **only the PVP is actually taught as suitable and efficiently used as crystallization inhibitor**.

Therefore, the skilled person, at the time the invention was made, only knew from Kanios at least two unlimited lists of compounds to consider.

Further to what is above, the two following publications should also be considered:

A) Summary Report EMEA – Rifaximin (Extension to topical use) May 1998

B) Berlo et al. "A prospective study in healthy volunteers of the topical absorption of a 5% of rifaximin cream," Drugs Exp Clin Res 1994; 20(5): 205 – 8.

Both these documents clearly demonstrate that Rifaximin is not absorbed, i.e. does not pass the skin to be systemically delivered, since no detectable amounts have been found in blood and urine, thus **limiting the external use of Rifaximin to topical administration**.

This means that, at the time the invention was made, the skilled person was well aware of the fact that **Rifaximin cannot be transdermally administered**, as also reminded above by citing paragraph 0004 of the current application.

Therefore, he/she would have never considered Kanios in order to solve the problem of the administration of high level, constant in time, of concentration of Rifaximin in aqueous body fluids avoiding the intense red color that the same produces in the neighboring of the place of administration, since actually **Kanios gives a scientifically incorrect teaching**. Accordingly, the skilled person would have at most considered **Rifaximin** as **erroneously cited within the unlimited list of possible active agents transdermally deliverable.**

This confirms once again the reasoning provided in our previous response, where it has been argued that Kanios, notwithstanding the statement that "there is no limitation on the type of active agent that can be used," indeed only demonstrated the enablement of his teaching for hormones, specifically estradiol and norethindrone acetate. This is also in line with *in re Wands*,

8 USPQ2d 1400 (Fed. Cir. 1988), for which a number of factors should be proved to be fulfilled in order to meet the enablement requirement especially in chemistry, pharmaceuticals, and biotechnology, that are recognized unpredictable art fields.

In the outstanding Office Action, at page 5, last paragraph, the Examiner further asserts:

> "...it is noted that the features upon which applicant relies (i.e., high-level, constant in time, of concentration of rifaximin in aqueous body fluids avoiding the intense red color that it produces in the area surrounding the administration site) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)." [emphasis added]

The Applicants traverse this finding. As a matter of fact, the devices of the current invention allow the use of Rifaximin outside the intestine (e.g., in the oral and pharyngeal or nasal cavity, in the rectum and vagina), further allowing high level, constant in time, of concentration of Rifaximin in aqueous body fluids **avoiding the intense red color** that it produces in the neighboring of the place of administration. The Examiner refers to the above as "features" of the claimed device, not readable in the claims. However, **they are not features**, but indeed "**technical effects**" achieved by the suitable combination of the essential features already present in Claim 34.

The skilled person reading the currently pending Claim 34 has all the essential features of the device for solving the technical problem peculiarly raised by Rifaximin and for attaining the above further technical effects.

In this regard, the Applicants wonder why in the Claim 34 should be readable both the essential features and the results achieved therefrom, even considering that the latter as such have non-limiting character.

Said technical effects are direct outcome of the implementation of the device of Claim 34 having features expressly claimed, thus there is no basis for expecting to read in the claim also technical effects achieved and technical problem solved, since a claim should only include all the essential features enabling the skilled person to put into practice the teaching concerned. In this view, the Applicants are of the opinion that Claim 34 as currently pending is properly limited and defined.

In view of all the above arguments, it can be summarized, also according to our previous response, that:

- Kanios is in the field of transdermal delivery of drugs, whereas the current invention is in the field of topical administration of a specific antibiotic;

- Kanios gives **a scientifically incorrect teaching, when including Rifaximin in the unlimited list of transdermally deliverable drugs**, thus the skilled person would have definitely disregard the document as a whole as **unsuitable and absolutely unreliable**, also in view of the published studies herewith enclosed.

Accordingly, the Applicants are still persuaded that **the Examiner came to her conclusion on the basis of a hindsight reconstruction of the claimed invention, by having**

knowledge of the same. As a matter of fact, she arbitrarily isolated substance from said unlimited lists in Kanios in order to conveniently lead to the claimed invention.

In the outstanding Office Action, the Examiner states that:

> "...it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As discussed above, the selection of the active ingredient and polyvinyl alcohol as the crystallization inhibitor based on the disclosure of Kanios takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made so no improper hindsight reasoning was employed." [emphasis added]

The arguments given above clearly confirmed the Applicants' finding that **the Examiner indeed made an improper reconstruction of the claimed invention**, since conversely she does not take into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and included knowledge gleaned only from the Applicants' disclosure, at the same time **relying all the raised rejections on a scientifically incorrect teaching.**

For all the above reasons, the currently pending Claim 34 is deemed to be **not obvious** over Kanios.

The currently pending Claims 34 – 36, 38 – 42 and 44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Kanios** further in view of **Govil et al.** (US 4,908,213).

In the outstanding Office Action, the Examiner affirms that:

> "Govil was cited for its teachings regarding the physical structure of the adhesive, comprised of acrylic polymers, optionally containing active substance, that can be applied to the surface of polymeric materials such as PVA and PVP (see page 7, ¶ 4 of April 6, 2009 Office Action). Applicants have not presented any arguments as to why one of ordinary skill would not, in light of Kanios and Govil that both relate to **transdermal drug delivery system**, would not be taught that the bio-adhesive polymer (the acrylic polymer) could not be either homogenously mixed into the polymeric matrix (such as polyacrylates) as required in claim 42 and taught by both Kanios and Govil or applied to the surface of the polymeric matrix as taught by Govil." [emphasis added]

Thus, the Examiner acknowledged that also **Govil et al.** relate to a transdermal drug delivery system, as Kanios, and accordingly **do not pertain to the same field of endeavor as the current invention**, in view of the same arguments given above for Kanios.

As already pointed out in our previous response, Govil et al. disclose a transdermal drug delivery patch, in particular, a patch useful for the transdermal delivery of nicotine, comprising an antipruritic agent selected from the group consisting of bisabolol, oil of chamomile, chamazulene, allantoin, D-panthenol, glycyrrhetenic acid, corticosteroids and antihistamines.

In view of the fact that Kanios has been proved to be scientifically not reliable, **the above supposed combination of the two prior art documents is now even more groundless** and therefore the skilled person would have at most faced with Govil et al. alone.

However, the Applicants wonder why a skilled person would have considered Govil et al., wherein he/she would have never found any useful information for solving the technical

problem associated with the topical use of Rifaximin, indeed by facing with a document concerning a **patch comprising nicotine and at least one antipruritic compound useful for reducing or eliminating itching caused by the transdermal penetration of nicotine**.

The fact that an acrylic polymer can be present in said patch does not add anything useful for the skilled person, unless acknowledging a further hindsight reconstruction of the present invention.

This is why the Applicants are convinced that the currently pending **Claim 34** is also **not obvious** over Kanios in view of Govil et al.

The currently pending Claims 34 – 36, 38 – 42, 44 and 45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable also over **Kanios** further in view of **Wharton** (US 6,194,455).

Wharton discloses a "method of preventing a nascent herpes outbreak from developing into a herpes ulcer, comprising the topical administration of a composition as a prophylactic comprising sucralfate and lidocaine in a weight:weight ratio of from about 500:1 to about 200:1, respectively, and a pharmaceutically effective amount of an antibiotic, in a pharmaceutically acceptable carrier to a site identified as a nascent herpes outbreak." (see Claim 1) [emphasis added]

Also this document **clearly and expressly does not pertain to the same field of**

endeavor of the current invention.

In the Examiner's opinion, "Wharton is a method, that method utilizes a topical composition for the delivery of active ingredient" and "Wharton was cited to show that the specific combination of an antibiotic with another antibiotic and/or an anti-inflammatory and/or pain reliever and/or anesthetic drug was known in the art and set forth reasons as to why such a combination (prevent infection and relieve pain, 8 – 9 of April 6, 2009 Office Action) would be selected from the possible combinations that exist for the active ingredients presented in Kanios."

As above reminded, Kanios has been proved to be scientifically not reliable, **the above supposed combination of the two prior art documents is now even more groundless** and therefore the skilled person would have at most faced with Wharton alone.

Actually, Wharton does not generally disclose a combination of "an antibiotic with another antibiotic and/or an anti-inflammatory and/or pain reliever and/or anaesthetic drug," but only sucralfate *and* lidocaine *and* a pharmaceutically effective amount of an antibiotic for preventing a nascent herpes outbreak from developing into a herpes ulcer. This is indeed the teaching of Wharton as a whole, even if the Examiner tried to broaden and decontextualize the same in order to justify her rejection.

Therefore, in view of the fact that chemistry, pharmaceuticals, and biotechnology are recognized unpredictable art fields, the Applicants wonder why the skilled person would have

taken Wharton into consideration for solving the technical problem associated with the topical use of Rifaximin.

Accordingly, the currently pending **Claim 34** is also **not obvious** over Kanios in view of Wharton.

For the above reasons, the Applicant is convinced that the device as set forth in the currently pending **Claim 34** is **not obvious** over the cited prior art documents, either taken alone or combined with each other.

Therefore, Applicants feel that the application as currently pending is in condition for allowance on the grounds that the arguments provided fully overcome the objections raised in the outstanding Office Action.

Respectfully submitted,

6/3/10
Date

Paul D. Greeley
Attorney for Applicants
Reg. No. 31,019
Ohlandt Greeley Ruggiero & Perle, LLP
One Landmark Square, 10th Floor
Stamford, CT 06901
Tel: (203) 327-4500
Fax: (203) 327-6401